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Bioorganic & Medicinal Chemistry Letters 18 (2008) 523–526
Bioorganic & Medicinal Chemistry Letters

Antiproliferative effects of dibenzocyclooctadiene lignans isolated from *Schisandra chinensis* in human cancer cells

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Received 12 October 2007; revised 17 November 2007; accepted 21 November 2007
Available online 28 November 2007

Abstract—Dibenzocyclooctadiene lignans isolated from *Schisandra chinensis* showed antiproliferative effects in various human cancer cells. The methoxy groups at C-3, C-4, C-3′, and C-4′, the hydroxyl group at C-8′, and the stereo-configuration of the biphenyl ring and the angeloyl group might have influence on these activities. Additional studies indicate that one of mechanism of action of an active compound schizantherin C in A549 human lung cancer cells was related to the inhibition of cell cycle progression in G0/G1 phase.

Schisandra chinensis (Turcz.) Baill. (Schisandraceae) is widely distributed in northeast Asia (Korea, China, and Japan) and eastern parts of Russia.[1] The fruit of *S. chinensis* was traditionally used in the alleviation or treatment of diseases due to deficiency of lung, heart and kidney, imbalance of Yin and Yang, and impairment of Qi, such as chronic cough, asthma, spontaneous sweating, palpitation, spermatorrhea, diabetes, insomnia, and forgetfulness.[1,2] Phytochemical studies for the isolation of constituents of *S. chinensis* have been extensively performed since 1970s. Various reports suggested that major bioactive constituents of *S. chinensis* were lignans belong to the dibenzocyclooctadiene type (Fig. 1).[3]

It has been reported that dibenzocyclooctadiene lignans possess hepatoprotective, antiviral, antioxidant, cytotoxic, and cancer chemopreventive activities.[1,4–10] The aqueous extract of *S. chinensis* restored hepatic drug metabolism in a CCl_4-induced hepatotoxicity model.[4] Gomisin B, gomisin G, and (+)-gomisin K_3 suppressed the formation of surface antigen or e antigen of human type B hepatitis virus.[5] Gomisin G and other related dibenzocyclooctadiene lignans showed anti-HIV activities.[6] The structure–activity relationships on the antioxidant and platelet-activating factor (PAF) antagonistic potential were also reported.[7,8] In particular, together with the range of non-cytotoxic concentration, gomisin A, schisandrin A and B, and schisantherin A restored cytotoxic activities of anticancer agents in multidrug-resistant human cancer cells, and schisandrin B selectively enhanced

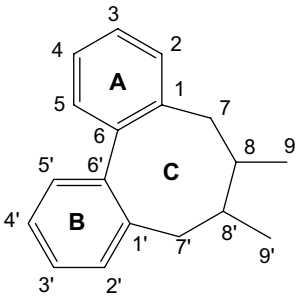

Figure 1. Chemical structures of C_{18}-dibenzocyclooctadiene.

Keywords: Dibenzocyclooctadiene lignan; Schisantherin C; Antiproliferation; Cancer; Cell cycle arrest; A549.
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doi:10.1016/j.bmcl.2007.11.082

cytotoxic and proapoptotic effects of doxorubicin.[9–11] In addition, schisantherin G and propinquanin E were cytotoxic in human cancer cells,[12] and gomisin A inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced tumor formation in a two-stage mouse carcinogenesis model.[13] These findings imply anticancer and cancer chemopreventive potential of dibenzocyclooctadiene lignans. However, previous studies focused on only one or some lignans. Although schisandrin B induced caspase-3-dependent apoptosis in human hepatoma cells,[14] the mechanisms underlying antiproliferative effects of dibenzocyclooctadiene lignans in human cancer cells have not been studied well. In this study, with the dibenzocyclooctadiene lignans isolated from the fruits of *S. chinensis*, we made an attempt to find the structural requirement for the antiproliferative effect in a panel of several human cancer cell lines (Fig. 2).[15] The mechanism of action of an active compound was also investigated.

Primarily, the inhibitory effects of dibenzocyclooctadiene lignans on the proliferation were evaluated in cultured various human cancer cells (MDA-MB-231, breast cancer (ER−); T47D, breast cancer (ER+); SK-HEP-1, hepatoma; SNU-638, stomach cancer; HCT-15, colon cancer; K562, leukemia; A549, lung cancer). Cells were treated with various concentrations of dibenzocyclooctadiene lignans for 72 h, and their antiproliferative effects were evaluated using MTT (K562) or SRB (other cell lines) assay.[16] Some dibenzocyclooctadiene lignans from *S. chinensis* showed the growth inhibitory effects against several cancer cells (Table 1). Especially, schizandrin, schisantherin C, and gomisin N showed the effective antiproliferative activities in most of tested cancer cell lines with the IC_{50} values ranging 10–70 μM. In addition, active compounds exhibited relatively more potent inhibitory effects toward T47D (ER+) cells compared with those of MDA-MB-231 (ER−) cells. From comparison of their structures with activities, the structural necessity for the antiproliferative effect is suggested as follows. First, the substitution groups of A and B rings might have influence on the antiproliferative activity of dibenzocyclooctadiene lignans in cancer cells. The compounds with the methylenedioxy group at C-3 and C-4 (A ring) or C-3′ and C-4′ (B ring) tend to show less potent activities than those with methoxy groups at the same positions in comparison of gomisin A and schizandrin, wuweizisu B and schisandrin A, and wuweizisu C and gomisin N, respectively. In addition, the introduction of hydroxyl group at C-8′ seems to be influential and generally enhances the activity exampled with gomisin A and wuweizisu B, and schizandrin and schisandrin A, respectively. Second, the stereo-configuration of rings or side groups might be also an important factor for determining the antiproliferative potential. Compared with gomisin B, schisantherin C, and gomisin C, the stereo-configuration of the hydroxyl group at C-8′ and the angeloyl group at C-7′ plays an important role in the antiproliferative effect. In case of possessing same side groups, the compound with *R*-biphenyl configuration (for example, wuweizisu B) is less potent than one with *S*-biphenyl configuration (gomisin N).

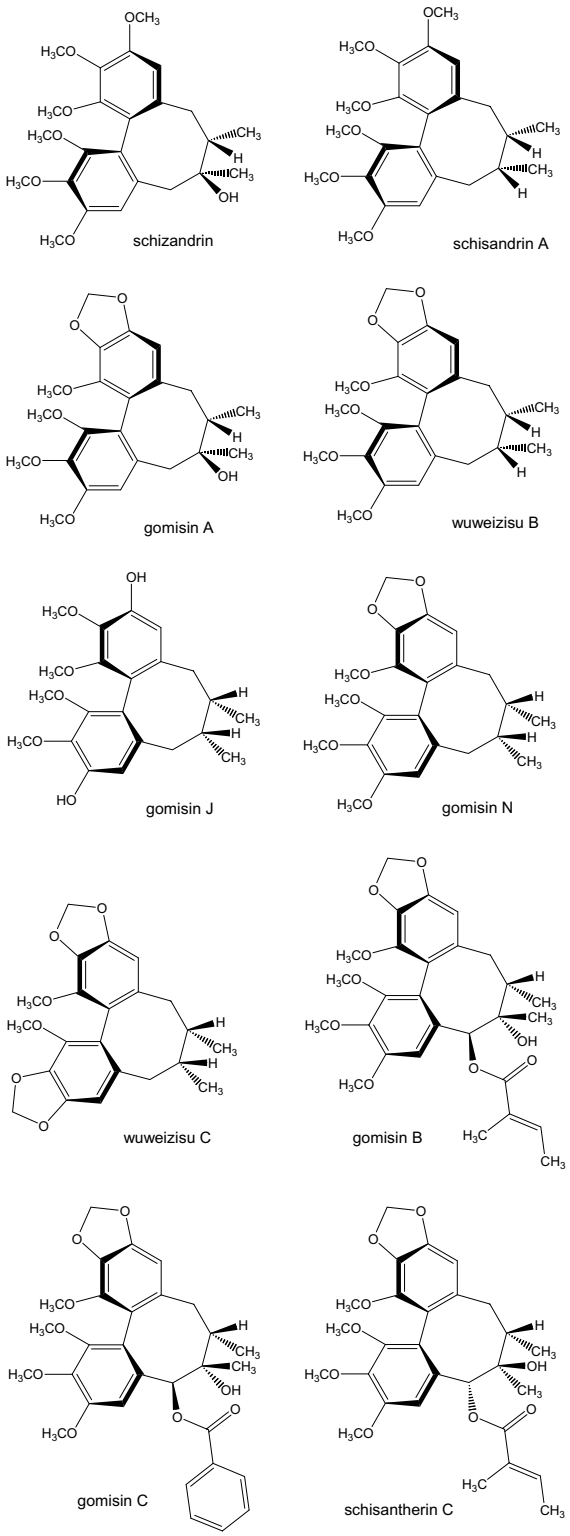

Figure 2. Chemical structures of dibenzocyclooctadiene lignans from *S. chinensis*.

As shown in Table 1, among the tested compounds, schisantherin C showed the most potent inhibitory effect in all of tested human cancer cells. Since schisantherin C was equally effective in A549 and HCT-15 cells, we further investigated the antiproliferative mechanism of